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Maternal hyperthyroidism after intrauterine insemination due to hypertrophic action of human chorionic gonadotropin: a case report

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Summary

Purpose of investigation: To report a rare case of maternal hyperthyroidism after intrauterine insemination due to hypertrophic action of hCG. *Materials and Methods:* A 36-year-old woman after successful intrauterine insemination and triplet pregnancy, developed hyperthyroidism with resistance to medical treatment. *Results:* All signs of hyperthyroidism resolved and the results of thyroid function tests returned to normal without any medication after embryo meiosis. *Conclusions:* De novo maternal hyperthyroidism may develop during pregnancy as a result of pathological stimulation of the thyroid gland from the high levels of hCG hormone that can be seen in multiple pregnancies. The risk of hyperthyroidism is related to the number of fetuses. Reversibility of symptomatology can be seen after fetal reduction of multiple pregnancies.

Key words: Thyrotropic action of hCG; Multiple pregnancy; Thyroidal hyperstimulation; Embryo meiosis; Maternal hyperthyroidism.

Introduction

Normal thyroid function is very important during pregnancy. Severe consequences for the mother and the fetus may result if hyperthyroidism or hypothyroidism is established. The increased levels of beta-hCG during the first trimester of pregnancy stimulate the thyroid gland. When the levels of beta hCG are high, during the first trimester of a normal pregnancy, the levels of thyroid stimulating hormone (TSH) are suppressed. This is explained by the fact that the increased levels of beta-hCG causes increased secretion of triiodothyronine (T_3) and thyroxine (T_4), resulting in suppression of TSH [1]. The levels of T_3, (T_4), and thyroxine binding globulin (TBG) increase more than 50% in pregnancy [2]. The TSH concentration in the first trimester of pregnancy decreases, while in the second and the third trimesters, TSH increases normal levels [2]. In the first trimester of pregnancy, maternal T_4 crosses the placenta. The fetal thyroid gland is not functional until the 12th week of gestation, unlike fetal thyroid hormone receptors which are functional earlier. Hypothyroidism occurs in 3% of pregnant women, while hyperthyroidism occurs in less than 1% of them [2]. Hyperthyroidism has serious consequences for the mother and the fetus, such as increased rates of miscarriages or premature births, preeclampsia, tachycardia or congestive heart failure for the mother, early fetal death or retarded development of the neurological system of the fetus, if it is not diagnosed early and not treated properly [3]. HCG is a glycoprotein whose structure is similar to TSH [4, 5].

Case Report

This is a rare case of 36-year-old woman submitted to intrauterine insemination with gonadotropin stimulation. The reason of infertility was idiopathic. Her history was unremarkable. She was married and was attempting to become pregnant for almost two years. During screening for infertility, free T_3 concentration was 2.9 pg/ml (normal 2−4.4 pg/ml), free T_4 concentration was 1.4 pg/ml (normal 0.93−1.7 pg/ml), and TSH concentration was 2.09 μIU/mI (normal 0.27−4.7 μIU/mI). The levels of prolactin, estradiol, progesterone, follicle stimulating hormone, luteinizing hormone, and finally free testosterone hormone in blood were normal. Anti-Müllerian hormone was increased. Controlled ovarian stimulation (COS) was performed by administration of recombinant human FSH, with starting dose of 75 IU/d on day 4 of the cycle for seven days, subcutaneously. She developed one follicle and ovulation was induced at follicle size of 18 mm using 250 IU of choriogonadotropin alfa. Thirty-six hours intrauterine insemination was performed. The first attempt of intrauterine insemination was not successful and after a period of two months, a second attempt was performed using 112.5 IU of recombinant FSH. Then, she developed three follicles and 250 IU of choriogonado-tropin alfa was given at follicular size of 18 mm. Following an unsuccessful second attempt, diagnostic hysteroscopy was performed. Hysteroscopy revealed the presence of incomplete septum that was restored using scissors and oral contraceptive pill was prescribed for the following month. Three months later she performed a new attempt for intrauterine insemination. The ovarian controlled stimulation was done on the same dose of recombinant human FSH (112.5 IU) as previously. Three follicles of 18 mm and one of 13 mm were present at the day of ovulation induction with 250 IU of choriogonadotropin alfa and 36 hours later the intrauterine insemination was performed.

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Results

This procedure resulted in triplet pregnancy. The serum concentration for beta-hCG at six weeks of pregnancy was 12,003 U/L (normal < five U/L). In the first two weeks of pregnancy the patient developed symptoms of hyperthyroidism: free T_3 concentration was more than 31.2 pmol/l (normal 3.5−8.3 pmol/l), free T_4 concentration greater than 38.09 pmol/l (normal 10.6−19.4 pmol/l), and TSH concentration less than 0.02 μIU/mI. The concentration of microsomal and antithyroglobulin antibodies were within normal limit. Initially she was treated with propylthiouracil 50 mg three times per day. The thyroid function did not yield to normal, free T_3 and free T_4 (fT_3: 8.32 pmol/l and fT_4: 35.7 pmol/l), TSH concentration was lower than 0.05 μIU/ml. The patient continued to demonstrate symptoms of hyperthyroidism such as tachycardia, weight loss, and sweating. The dose of propylthiouracil 50 mg was increased on four times per day. Even at a higher dose of propylthiouracil, the symptoms persisted and the thyroid hormone levels remained elevated. After an increase of the dose of propylthiouracil to 300 mg per day, the serum concentration of thyroid hormones remained elevated. During progression of pregnancy and development of placentas, the production of hCG continues to rise in excess. Concurrently with the increase of beta-hCG, the thyroid hormone concentration remained increased. Even when the dose of propylthiouracil reached 450 mg per day, the symptoms of hyperthyroidism persisted. On the 12th week of gestation the patient underwent amnioparacentesis and embryo meiosis to twin pregnancy. The results were immediate. As soon as the embryo meiosis took place, the symptoms of hyperthyroidism began to abate. Even the serum results of thyroid function decreased to normal. Ten weeks later, after the embryo meiosis, all signs of hyperthyroidism resolved, the thyroid function tests returned to normal, and the patient no longer needed to be treated with propylthiouracil.

Discussion

HCG is a human glycoprotein hormone. As human glycoproteins hormones, are hCG, LH, TSH, and FSH [6,7]. These hormones are heterodimers, consisting of a common α-subunit and a receptor-specific β-subunit, and confer activity by binding to their respective G protein-coupled receptors (GPCRs) [8, 9]. Recent trials have clarified the structural homology not only in the hCG and TSH molecules, but also in their receptors, and this homology suggests the basis for the reactivity of hCG with the TSH receptor. If intact hCG were as potent as hLH in regards to its thyrotrophic activity, most pregnant women would become thyrotoxic. Deglycosylation and/or desialylation of hCG enhances its thyrotropic potency. The thyroid gland of normal pregnant women may be stimulated by hCG to secrete slightly excessive quantities of T_4 and induce a slight suppression of TSH, perhaps being about one mU/L less than nongravid levels, but not high enough to induce overt hyperthyroidism. Maternal thyroid glands may secrete more thyroid hormone during early pregnancy in response to the thyrotropic activity of hCG that overrides the normal operation of the hypothalamic-pituitary-thyroid feedback system. To understand the thyrotropic action of hCG, it is necessary to know whether hCG activates the same domain of the TSH receptor as does TSH and therefore further studies are needed to answer this question. In multiple pregnancies, the multiple placentas produces larger amounts of hCG for a longer period of time in comparison with single pregnancies. The persisting long-term hCG overproduction and the long-term exposure of the thyroid gland to large amounts of hCG are responsible for thyroidal hyperstimulation.

Conclusion

A correlation between triplet pregnancy and indirectly hCG levels and maternal hyperthyroidism was found with reversibility of symptomatology and laboratory values with fetal reduction from a triplet to twin pregnancy. It seems that very high levels of hCG can stimulate the receptors of TSH to become intracellular, reducing its circulating level and making this type of hyperthyroidism persistent to medical treatment. This assumption complies with the evolution of this case, because as soon as the present patient had embryo meiosis, her hyperthyroidism symptoms were resolved.

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